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Discovery of 1-(4-phenoxypiperidin-1-yl)-2-arylaminoethanone stearoyl-CoA desaturase 1 inhibitors

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Abstract—A series of novel stearoyl-CoA desaturase 1 (SCD1) inhibitors were identified by scaffold design based on known SCD1 inhibitors. Large structural changes were made leading to multiple analogs with comparable or improved potency. This approach is valuable for generation of proprietary compounds without conducting a costly high-throughput screening.

The quality of lead compounds and druggability of biological targets dictate the lead optimization strategies.[1] When the lead is a literature compound, one needs to drastically change its structure to secure an unquestionable intellectual property (IP) position.[2] Scaffold hopping is a computational technique that identifies compounds with different skeletons that match the predefined pharmacophore in a given database.[3] Medicinal chemists can also design and synthesize novel molecules with a different scaffold from the lead compound and nonetheless show similar or improved properties. Here we report a successful application of this strategy in the discovery of a series of potent stearoyl-CoA desaturase 1 (SCD1) inhibitors based on competitor's compounds. This approach is cost and time effective because no internal high-throughput screening is needed and is particularly desirable for those drug discovery programs without screening capacity.

SCD1 is a microsomal enzyme that catalyzes the rate-limiting step in the biosynthesis of monounsaturated fatty acids from saturated fatty acids.[4–6] It plays an important role in lipid metabolism[7] and body weight control.[8] Reduced adiposity, increased insulin sensitivity, and resistance to diet-induced obesity have been observed in SCD1 deficient Asebia mice[9] and SCD1 knockout mice.[10,11] Inhibition of SCD1 activity via antisense oligonucleotides in diet-induced obese (DIO) mice resulted in lower adiposity and higher energy expenditure.[12] Higher SCD1 activity has been linked to elevated plasma triglyceride level in humans.[13] Small molecule SCD1 inhibitors are expected to be beneficial in treating obesity and the related metabolic syndrome.

When we started the program, the only known class of SCD1 inhibitors was piperidyl arylcarboxamides reported by scientists from Xenon Pharmaceuticals (e.g., compound **1**, Figure 1).[14–19] To change the molecular skeleton of **1** and yet retain its biological activity, we first needed to hypothesize a pharmacophore model. Since the structure of SCD1 was not known, only ligand-based design was possible. Compound **1** was a fairly efficient ligand for SCD1 considering its size, molecular complexity, and level of functionalization. The pyridazine ring in **1** could be replaced by other heterocycles such as isomeric pyridines, pyrimidines, and pyrazines without losing much of the activity, suggesting this region might tolerate larger structural changes. The process of deriving the pharmacophore **4** is outlined in Figure 1. Structure **2** has similar functional groups to those in lead **1** although their most stable conformations would be quite different. Structure **3** is a close analog of **1** and **2** that retains all of their heteroatoms and continuity of sp^2 hybridized carbon atoms if linker ('L') is an aromatic ring. To turn **3** into a stable molecule, pharmacophore **4** was envisioned. In structure **4**, a more flexible

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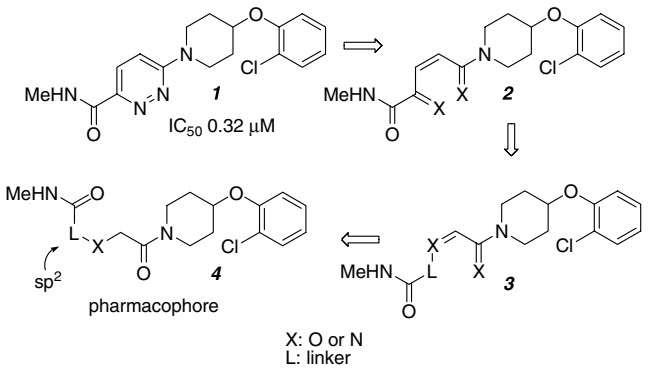
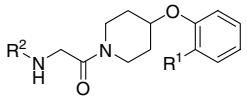


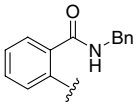
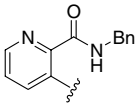
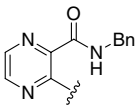
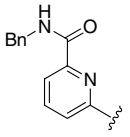
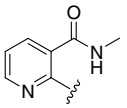
Figure 1. The logic of generating pharmacophore **4**.

and hydrophobic sp^3 hybridized carbon atom is introduced resulting in a large conformational change and an increase of hydrophobicity. To accommodate this new feature, screening several polar aromatic linkers ('L') was deemed necessary to find an optimal scaffold.

Thus several aromatic linkers ('L' in **4**) were evaluated first and the results are summarized in Table 1. Based on the SAR information on **1**, the 2-trifluoromethyl and 2-chlorophenoxy groups on the right hand side and the methyl and benzyl amides at the left hand side were very similar and they were interchangeably used depending on the commercial availability of the starting materials and chemistry used. A benzene analog (inhibitor **5**) showed a weaker potency than **1**.[20] The core structure of **5** has more carbon atoms than **1**, which might lead to unfavorable interactions and desolvation energy for binding. Indeed, a pyridine derivative **6a** showed a comparable potency to **1** and a pyrazine analog **7a** demonstrated an even stronger inhibitory activity than the lead compound **1**. The isomeric pyridine analogs **8** and **9** were much less active.

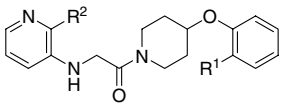
Table 1. Evaluation of different aromatic linkers ('L' in **4**, Fig. 1)



No.	R^1	R^2	IC_{50} (μM)
5	Cl		0.58
6a	Cl		0.56 ± 0.27
7a	Cl		0.14 ± 0.0
8	CF_3		7.3 ± 0.0
9	CF_3		>1

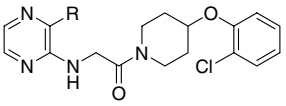
Having identified two new scaffolds (those of **6a** and **7a**, respectively), more thorough SAR investigations were initiated to search for more potent inhibitors. As summarized in Tables 2 and 3, a series of 2,3-substituted pyridine and pyrazine carboxylamides were synthesized and assayed. Although, most analogs showed good potency against human SCD1, a relatively flat SAR was observed with primary or short secondary amides being slightly favored. Tertiary amides and branched secondary amides (e.g., **6j** and **6k** in comparison to **6c** and **6e**, Table 2) were much less favorable. The alkyl portion

Table 2. SAR of pyridine-based SCD1 inhibitors



No.	R^1	R^2	IC_{50} (μM)
6a	Cl	CONHBn	0.56 ± 0.27
6b	CF_3	$CONH_2$	0.090 ± 0.12
6c	CF_3	CONHMe	0.097 ± 0.017
6d	CF_3	CONHEt	0.11 ± 0.085
6e	CF_3	CONHPr	0.39 ± 0.14
6f	CF_3	$CONH(CH_2)_2OH$	0.12 ± 0.021
6g	CF_3	$CONHCH_2$(*m*-pyridyl)	0.43 ± 0.38
6h	CF_3	$CONHCH_2$(*p*-pyridyl)	0.35 ± 0.35
6i	CF_3	$CONH(CH_2)_2Ph$	0.78
6j	CF_3	$CONMe_2$	>10
6k	CF_3	CONH(*c*-pentyl)	>10

Table 3. SAR of pyrazine-based SCD1 inhibitors



No.	R	IC_{50} (μM)
7a	CONHBn	0.14 ± 0.00
7b	$CONH_2$	0.094 ± 0.033
7c	CONHMe	0.051 ± 0.040
7d	CONHEt	0.039 ± 0.060
7e	CONH(iBu)	0.26 ± 0.22
7f	$CONH(CH_2)_2OH$	0.10 ± 0.008
7g	$CONHCH_2$(*o*-pyridyl)	0.11 ± 0.11
7h	$CONHCH_2$(*m*-pyridyl)	0.099 ± 0.11
7i	$CONHCH_2$(*p*-pyridyl)	0.11 ± 0.017
7j	CONHPh	0.55 ± 0.45
7k	CO_2Me	0.039 ± 0.020
7l	CHO	0.21 ± 0.049
7m	CN	0.34 ± 0.33
7n	Cl	0.030 ± 0.0007